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Robyn N. D'Agostino

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As technology continues to advance at an exponential rate (Kurzweil, 2006), it is only natural that these advancements will be utilized by humans in ways to enhance our biology. Deep brain stimulation (DBS), a surgical procedure involving the insertion of an electrode into the brain, fed by a thin wire and implantable pulse generator (IPG), is an increasingly common human application of technological advancements. Initially developed in 1987 by Dr. Alim-Louis Benabid, DBS was first approved by the Food and Drug Administration (FDA) in the United States in 1997 (Okun & Zeilman, 2014). In DBS surgery, leads are implanted either unilaterally (on one side of the brain), or bilaterally (on both sides), and are connected to the IPG. Programmed currents are released from the IPG, stimulating the target brain area to improve symptoms of an underlying condition (Okun & Zeilman, 2014). The IPG can be adjusted externally, using a programmer, by holding the device over the area of the implanted IPG—usually the chest or abdomen. Currently, DBS is an FDA-approved treatment for dystonia, essential tremor, and Parkinson's disease (Miocinovic, Somayajula, Chitnis & Vitek, 2013). Its current intended purpose is to provide relief of symptoms for patients whose symptoms cannot be controlled with medications (Miocinovic et al., 2013), and is most often used to treat Parkinson's disease (PD) symptoms.

PD is a degenerative disorder that belongs to the larger group of movement disorders. It is characterized by four primary symptoms: tremor, rigidity, bradykinesia, and postural

instability, which involve trembling in hands, arms and legs, stiffness of the limbs and trunk, slowness of movement, and impaired balance, respectively ("Parkinson's disease: Hope through research"). As a central nervous system (CNS) degenerative disorder, the symptoms of PD are exacerbated by death or impairment of neurons. The area most commonly affected in PD is the basal ganglia, a region of the brain involved with movement. Specifically, a loss of dopaminergic neurons in the substantia nigra is noted in PD (Bernheimer, Birkmayer, Hornykiewicz, Jellinger & Seitelberger, 1973). This loss of dopaminergic neurons is thought to cause the impaired motor functions commonly observed in PD (German, Manaye, Smith, Woodward & Saper, 1989; Hirsch, Graybiel & Agid, 1988).

DBS, when used to treat PD, is implanted to stimulate areas of the basal ganglia; specifically, the subthalamic nucleus or global pallidus internus (Figure 1).

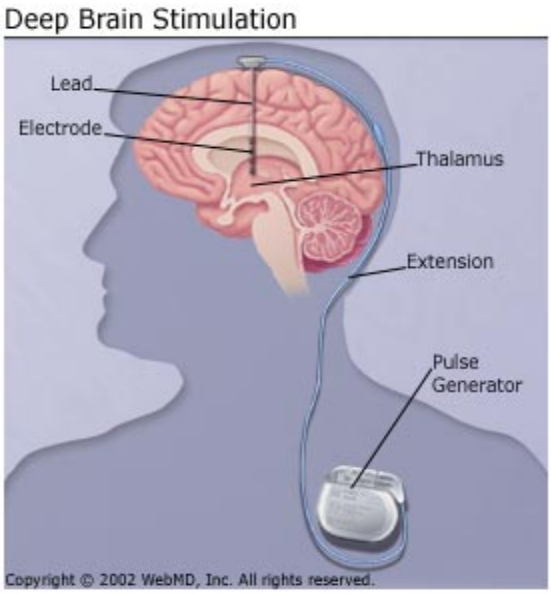

Figure 1: Illustration of result of DBS surgery. Showing implantable pulse generator (IPG), extension and electrode inserted into the thalamus. (Figure from *Deep Brain Stimulation, n.d.* http://www.webmd.com/parkinsons-disease/guide/dbs-parkinsons)

The effects of DBS on motor symptoms are dependent on the DBS frequency, as noted by Benabid, Pollak, Hoffmann, Gervason, Hommel, Perret, de Rougemont and Gao (1991). Further findings by Moro, Esselink, Xie, Hommel, Benabid, and Pollak (2002a) confirm prior research in a study to discover how varying the electrical parameters of DBS can have varying impact on motor symptoms in PD. Moro et al. (2002a) show that beneficial effects increase as frequency of DBS increases, further supporting prior research indicating that DBS effects on motor function are dependent on stimulation frequency. While the effects of DBS on salient symptoms of movement disorders are known, the exact mechanisms by which they function remain a mystery (McIntyre, Grill, Sherman & Thakor, 2004).

Scientists continue to focus on identifying these mechanisms, and have proposed a hypothesis known as the stimulation-induced modulation of pathological network activity. Under this hypothesis, extracellular stimulation of neurons result in a stimulation-induced action potential in the axon, rather than the cell body (McIntyre et al., 2004). Intracellular stimulation to the cell body of thalamocortical (TC) neurons resulted in a generation of action potentials 1:1 with the stimulus frequency, which were generated in the cell body and transmitted down the axon. Extracellular stimulation at high frequencies; however, showed independent firing of the cell body and axon (Figure 2).

These results support the stimulation-induced modulation hypothesis and point towards the idea that DBS exerts its effects by overriding the irregular neuronal firing activity in PD by replacing it with regular, stimulus-induced firing patterns (McIntyre et al., 2004).

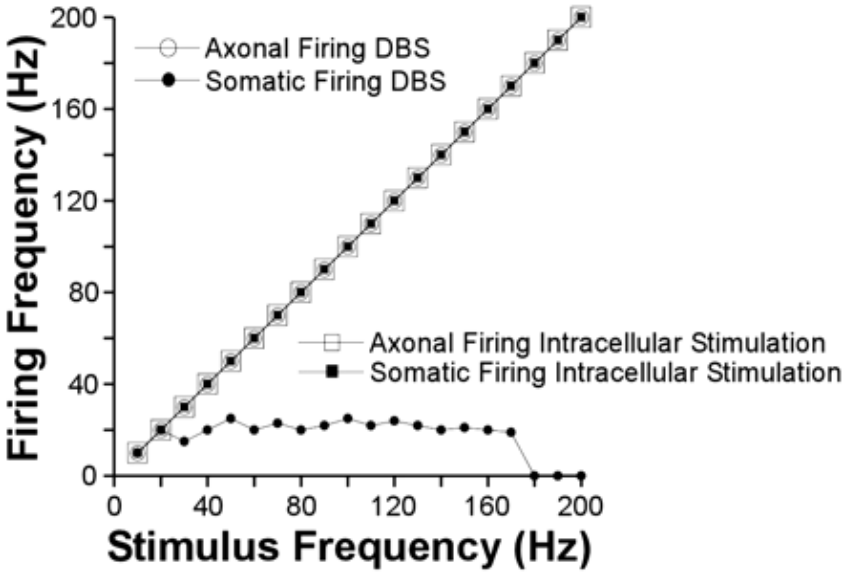

Figure 2: Axonal and somatic firing frequency of TC relay neuron in response to intracellular or extracellular (DBS) stimulation. Intracellular stimulation generated axon potentials involving transmission from the cell body down the axon at a 1:1 ratio with stimulation frequency. Extracellular DBS stimulation resulted in independent firing of the neuron at high frequencies, with only the axon responding in a 1:1 ratio. The cell body was unable to follow. (Figure from: McIntyre et al., 2004, http://jn.physiology.org/content/91/4/1457.long)

In addition to understanding the mechanism of action for DBS treatment in PD, researchers are investigating different effects DBS can have for patients. Van Hartevelt, Cabral, Deco, Moller, Green, Aziz and Kringelbach (2014) investigate the effects of post-operative, long term DBS on a 45-year-old female. In this rare case, van Hartevelt et al. (2014) were able to acquire preoperative and postoperative MRI scans, assisting in their research. Despite postoperative artefact in the left hemisphere, van Hartevelt et al. (2014) were able to observe an increase in connection density, nodal efficacy and bifurcation point postoperatively. These results suggest DBS causes local changes in specific brain regions, and that these local structural changes influence functional, global, connectivity. An increase in the bifurcation point, or the point at

which unstable or chaotic neural activity results if neurons are stimulated further, indicates that DBS has restorative effects on structural connectivity (Figure 3) (van Hartevelt et al., 2014).

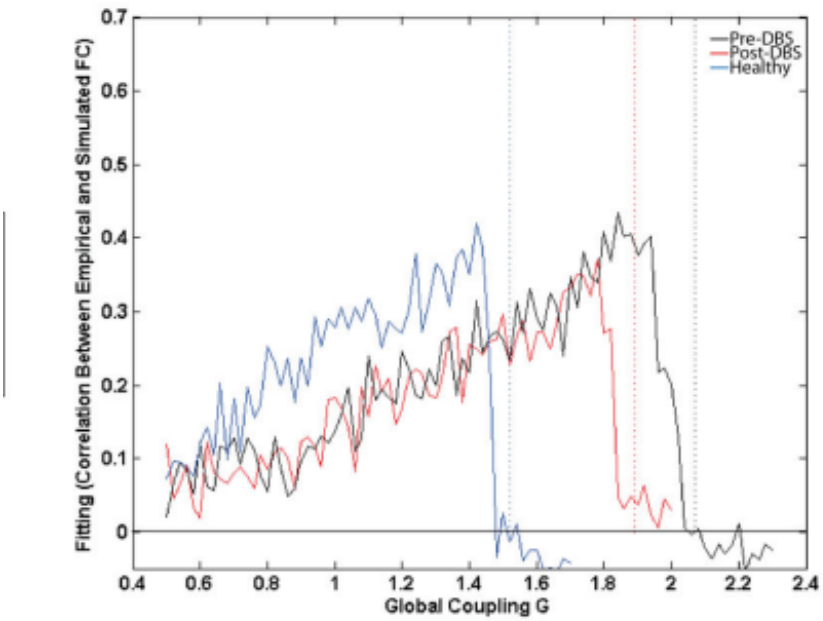

Figure 3: Description of the fitting of stimulated functional connectivity (FC) with post-DBS, pre-DBS, and healthy controls. Post-DBS is shown in red, pre-DBS in black, and healthy controls in blue. Vertical dashed lines indicate bifurcation points for each corresponding condition. Shifting of the post-DBS FC bifurcation point towards the healthy bifurcation point indicates potential recovery of the structural connectivity due to DBS. (Figure from: van Hartevelt et al., (2014), http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0086496)

Given that DBS has gradually developed since its invention in 1987, utilization of DBS to alleviate symptoms of PD appears to be an intentional merger of technology and biology. While the exact mechanism of action is not yet understood, the tangible effects are known (McIntyre et al., 2004; Moro et al., 2002a; van Hartevelt et al., 2014). While researchers work to identify mechanisms of DBS action, technology companies are working to develop more advanced DBS treatments, and improve the existing technology. These DBS disadvantages in need of improvement include the necessary, periodical replacement of IPG batteries, hardware

malfunction, as well as neuroimaging and electric and magnetic field complications (Joint, Nandi, Parkin, Gregory & Aziz, 2002; Kringelbach, Jenkinson, Owen & Aziz, 2007).

Despite potential drawbacks, DBS has several advantages including adjustable stimulation, continuous symptom relief and its accompanying medicinal reduction (Okun & Zeilman, 2014). DBS implants may be adjusted using a programmer device to identify the level of stimulation that best reduces individual symptoms (Okun & Zeilman, 2014). Additionally, while on, DBS provides continual symptom alleviation and allows for a decrease in the use of medicinal treatment and side effects (Moro, Esselink, Benabid & Pollak, 2002b; Okun & Zeilman, 2014).

DBS can be considered an irreversible merger, despite the possible removal of the IPG. The relief of symptoms experienced by patients is due to the continual stimulation provided by DBS and the IPG; for this reason, it is highly unlikely that a patient would electively remove their IPG (Obeso, Olanow, Rodriguez-Oroz, Krack, Kumar & Lang, 2001). In extreme cases, such as malfunction, removal may be an option; however, Parkinson's patients who are eligible for DBS are often at their last hope (Miocinovic et al., 2013; Okun & Zeilman, 2014), and would not electively remove a device responsible for relief of their symptoms.

The DBS hybrid system is continuing to advance, and does not appear to be slowing down. Efficacy of this system could be improved by making mechanical changes to the technology; for example, electrode advancements can lead to increased power efficiency. Segmented electrodes, specifically, delivered larger magnitudes of extracellular potentials. These electrodes required lower stimulation than solid electrodes to achieve neuronal activation levels (Wei & Grill, 2007). These improvements could be maximized by combining technological enhancements with increased biological selectivity—localizing the delivered current to specific

areas of neurons, rather than a general location in the brain (Wei & Grill, 2007). With the progression of technology and human intelligence will come a progression of technological, biological enhancements. DBS is the beginning of this movement, and will continue to evolve in future years.

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I have abided by the Wheaton College Honor Code in this work.
Robyn N. D'Agostino